

In the Specification:

Please delete the paragraph at page 4, lines 24-28 and replace it with the following paragraph:

*B*  
Thus, there still remains a need for a more effective anti-HIV oligonucleotide having therapeutic effects that are accompanied by fewer side effects, e.g., little cellular toxicity and reduced immunostimulatory response.

Please delete the paragraph at page 7, lines 24-31 and replace it with the following paragraph:

*B*  
In yet another aspect, the invention provides pharmaceutical formulations suitable for inhibiting and treating HIV-1 or HIV-2 infection and having reduced side effects such as immunogenicity. These formulations comprise at least one oligonucleotide in accordance with the invention in a pharmaceutically acceptable carrier.

Please delete the paragraph at page 7, line 33 to page 8, line 12 and replace it with the following paragraph:

*B*  
As used herein, a "pharmaceutically or physiologically acceptable carrier" includes any and all solvents (including but not limited to lactose), dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

Please delete the paragraph at page 8, line 14 to page 9, line 2 and replace it with the following paragraph:

*B4*

In another aspect, the invention provides a method of treating HIV-1 or HIV-2 infection in a mammal. In this method an oligonucleotide according to the invention is administered to the mammal in an amount effective to inhibit the proliferation of the virus. For purposes of the invention, the term "mammal" is meant to encompass primates and humans. In some embodiments, the oligonucleotide is orally administered to the mammal. The term "orally administered" refers to the provision of the formulation via the mouth through ingestion, or via some other part of the gastrointestinal system including the esophagus. In other embodiments, the oligonucleotide is administered via intravenous injection. In yet other embodiments, the oligonucleotide is administered colorectally. The term "colorectal administration" or "rectal administration" or "colorectally administered" refers to the provision of the pharmaceutical formulation of the invention to any part of the large intestine via surgical implantation, anal administration, or any other mode of placement therein.

Please delete the paragraph at page 11, lines 3-8 and replace it with the following paragraph:

*B5*

The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. The issued U.S. patents, allowed patent applications, and articles cited herein are hereby incorporated by reference.

Please delete the paragraph at page 20, lines 1-8 and replace it with the following paragraph:

*B6*

The oligonucleotides described herein are administered to the mammal in the form of therapeutic pharmaceutical formulations that are effective for treating virus infection. These pharmaceutical formulations may be administered in conjunction with other therapeutic agents, e.g., AZT and/or various protease inhibitors, to treat AIDS.

Please delete the paragraph at page 24, lines 10-20 and replace it with the following paragraph:

*B1*  
Administration of pharmaceutical compositions in accordance with the invention or to practice the method of the present invention can be carried out in a variety of conventional ways, such as by oral ingestion, enteral, colorectal, or transdermal administration, inhalation, sublingual administration, or cutaneous, subcutaneous, intramuscular, intraocular, intraperitoneal, or intravenous injection, or any other route of administration known in the art for administrating therapeutic agents.

Please delete the paragraph at page 25, line 22 to page 26, line 24 and replace it with the following paragraph:

*B2*  
When a therapeutically effective amount of composition of the invention is administered by injection, the synthetic oligonucleotide will preferably be in the form of a pyrogen-free, parenterally-acceptable, aqueous solution. The preparation of such parenterally-acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for injection should contain, in addition to the synthetic oligonucleotide, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art. The pharmaceutical formulation can be administered in bolus, continuous, or intermittent dosages, or in a combination of continuous and intermittent dosages, as determined by the physician and the degree and/or stage of illness of the patient. The duration of therapy using the pharmaceutical composition of the present invention will vary, depending on the unique characteristics of the oligonucleotide and the particular therapeutic effect to be achieved, the limitations inherent in the art of preparing such a therapeutic formulation for the treatment of humans, the severity of the disease being treated and the condition and potential idiosyncratic response of each

*B8*  
individual patient. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Please delete the paragraph at page 26, line 26 to page 27, line 3 and replace it with the following paragraph:

*B9*  
To determine the preclinical range of anti-HIV activity of various oligonucleotides of the invention (see TABLE 2), evaluations were performed with Oligo 12 (having SEQ ID NO:1), Oligo 32 (SEQ ID NO:3) and Oligo 41 (SEQ ID NO:6). These evaluations were performed to determine the activity of these compounds against a variety of wild type and drug-resistant strains of HIV-1, including both laboratory derived and low passage, clinical strains of virus and T-lymphocyte-tropic and monocyte-macrophage-tropic viruses such as those listed below in TABLE 3.

Please delete the text at page 27, line 26 and replace it with the following text:

*B10*  
SI - syncytium inducing

Please delete the paragraph at page 30, lines 30-33 and replace it with the following paragraph:

*B11*  
In another set of experiments, the bioavailability of Oligo 12 was examined *in vivo* and was found to be intravenously and orally bioavailable to rats and monkeys after a single dose.

**In the Claims:**

Please amend claims 1, 3, 6, 16, 18, 19, 20, and 21 as noted on Attachment 1. Please cancel claims 2 and 17 without prejudice or disclaimer of the subject matter claimed therein. As required by 37 C.F.R. § 1.121(c), the amended claims are rewritten with all changes included. In addition, as permitted under 37 C.F.R. § 1.121(c)(3), a clean version of all of the pending claims is submitted as Attachment 1. Also enclosed